

## KINETICS AND METABOLISM OF PARACETAMOL AND PHENACETIN

L.F. PRESCOTT

University Department of Therapeutics and Clinical Pharmacology, The Royal Infirmary,  
Edinburgh, UK

1 The rate of absorption of oral paracetamol depends on the rate of gastric emptying and is usually rapid and complete. The mean systemic availability is about 75%.

2 Paracetamol is extensively metabolized and the plasma half-life is 1.5–2.5 hours. About 55% and 30% of a therapeutic dose is excreted in the urine as glucuronide and sulphate conjugates, respectively, whereas mercapturic acid and cysteine conjugates (representing conversion to a potentially toxic intermediate metabolite) each account for some 4% of the dose. Paracetamol metabolism is age- and dose-dependent.

3 With hepatotoxic doses, paracetamol metabolism is impaired and the half-life prolonged. Sulphate conjugation is saturated and the proportion excreted as mercapturic acid and cysteine conjugates is increased.

4 The renal clearance of paracetamol depends on urine flow rate but not *pH*. The renal clearances of the glucuronide and sulphate conjugates often exceed the glomerular filtration rate and are independent of urine flow and *pH*.

5 Phenacetin absorption depends on formulation. It is extensively metabolized to paracetamol and minor metabolites are probably responsible for toxicity

### Paracetamol

PARACETAMOL (acetaminophen, *N*-acetyl-*p*-aminophenol, 4-hydroxyacetanilide) is a moderately water- and lipid-soluble weak organic acid. It has a *pK<sub>a</sub>* value of 9.5 and is therefore largely unionized over the physiological range of *pH*.

#### Absorption

Paracetamol is invariably taken orally. Absorption from the gastrointestinal tract is by passive transport (Bagnall, Kelleher, Walker & Losowsky, 1979) and there is only minor metabolism of the drug by the gastrointestinal mucosa in the rat (Josting, Winne & Bock, 1976). In man, paracetamol absorption is negligible from the stomach but very rapid from the small intestine and the rate of absorption therefore depends on the rate of gastric emptying (Heading, Nimmo, Prescott & Tothill, 1973). Absorption is slowed if gastric emptying is delayed by food, posture, disease and drugs such as propantheline and narcotic analgesics, but the total amount absorbed is not decreased (McGilveray & Mattok, 1972; Nimmo, Heading, Tothill & Prescott, 1973; Nimmo, Heading, Wilson, Tothill & Prescott, 1975; Nimmo & Prescott, 1978).

In fasting healthy subjects, absorption of paracetamol in solution is very rapid with peak plasma concentrations often occurring within 15–30 min of ingestion. Absorption from tablets is usually slower,

and in practical clinical conditions there may be as much as an 80-fold range in plasma concentrations 1 h after administration of a therapeutic dose (Prescott, 1974).

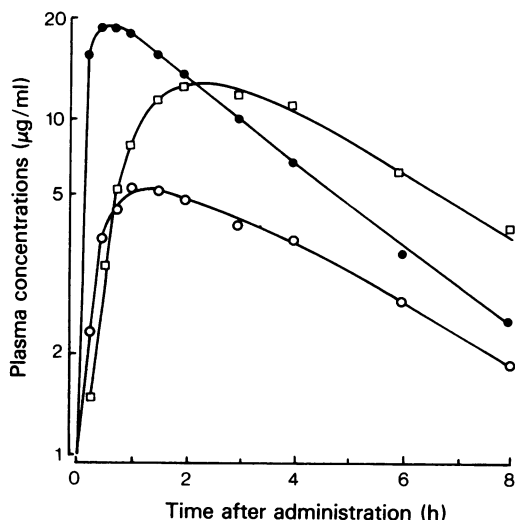
#### Distribution

Paracetamol is rapidly and relatively uniformly distributed in the tissues (Brodie & Axelrod, 1949). The ratio of concentrations in red blood cells and plasma is about 1.2:1 and binding to plasma proteins is insignificant (Gazzard, Ford-Hutchinson, Smith & Williams, 1973). The apparent volume of distribution of paracetamol in man is about 0.9 l/kg (see below).

#### Metabolism

Paracetamol is extensively metabolized and only 2–5% of a therapeutic dose is excreted unchanged in the urine. Although biotransformation occurs predominately in the liver, there may be some metabolism of the drug in the gut and kidney (Josting, Winne & Bock, 1976; Jones, Sundby, Ormstad & Orrenius, 1979; Mitchell, McMurtry, Statham & Nelson, 1977).

The major metabolites of paracetamol are the sulphate and glucuronide conjugates, but a minor



**Figure 1** Mean plasma concentrations of paracetamol (●;  $t_4=2.3$ ) and its sulphate (○) and glucuronide conjugates (□) (expressed as paracetamol equivalents) in 8 healthy subjects after an oral dose of 20 mg/kg.

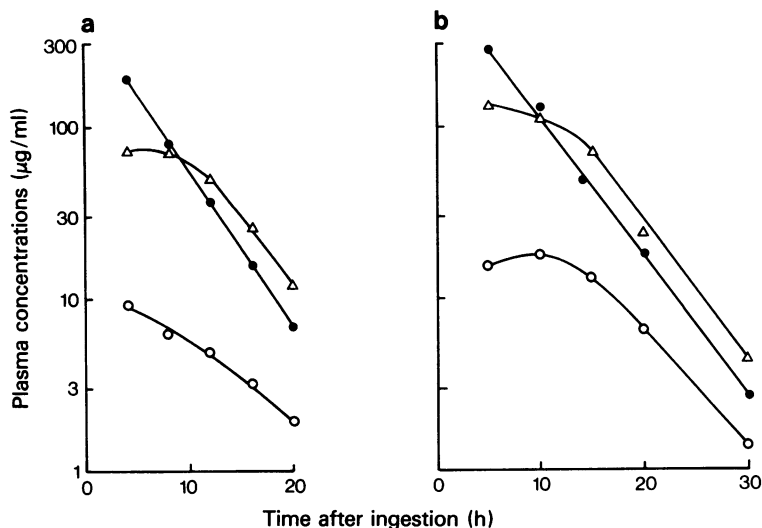
fraction is converted by hepatic mixed function oxidase to a highly reactive alkylating metabolite. This metabolite is normally rapidly inactivated by conjugation with reduced glutathione and eventually excreted in the urine as cysteine and mercapturic acid conjugates. Large doses of paracetamol cause acute hepatic necrosis as a result of depletion of glutathione and of covalent binding of the excess reactive metabolite to vital cell constituents (Mitchell, Jollow, Potter, Davis, Gillette & Brodie, 1973; Mitchell, Thorgeirsson, Potter, Jollow & Keiser, 1974). Paracetamol causes acute renal tubular necrosis by a similar mechanism and its toxicity is dependent on microsomal enzyme activity and glutathione availability (Mitchell *et al.*, 1977). In keeping with these mechanisms, liver damage and renal failure following paracetamol overdose can be prevented by early administration of sulphydryl compounds such as *N*-acetylcysteine (Prescott, Illingworth, Critchley, Stewart, Adam & Proudfoot, 1979). Other minor metabolites of paracetamol include conjugates of 3-methoxy-, 3-hydroxy- and 3-thiomethylparacetamol (Andrews, Bond, Burnett, Saunders & Watson, 1976; Klutch, Levin, Chang, Vane & Conney, 1978).

Paracetamol metabolism is age- and dose-dependent. In healthy young adults the plasma paracetamol half-life following a therapeutic dose is about 2 h (range 1.5–2.5 h), and about 4%, 30%, 55%, 4% and 4% of the dose is excreted in the urine in 24 h as unchanged paracetamol and its sulphate, glucuronide, cysteine and mercapturic acid

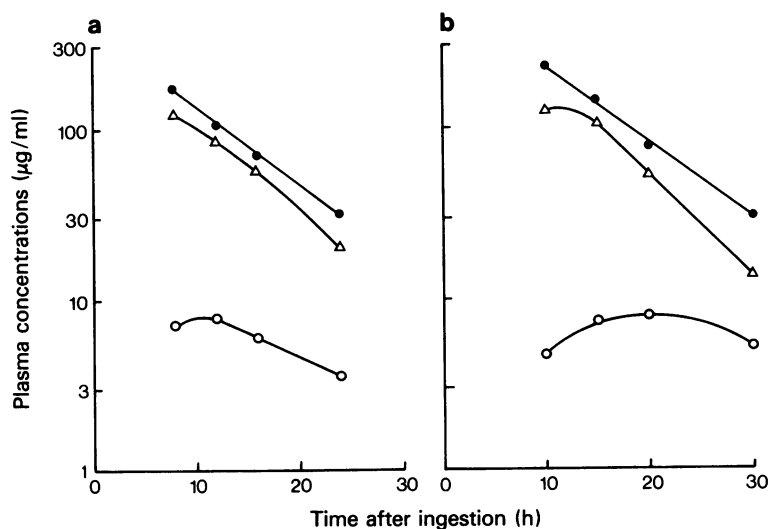
conjugates, respectively. In neonates and young children, however, glucuronide conjugation is deficient. The half-life is prolonged and sulphate conjugation is the dominant metabolic pathway (Levy, Khanna, Soda, Tsuzuki & Stern, 1975; Miller, Roberts & Fischer, 1976). Although it has been claimed that paracetamol metabolism is impaired in the elderly (Briant, Dorrington, Cleal & Williams, 1976), the mean plasma half-life (2.17 h) is well within the range reported in young adults by many investigators. The plasma paracetamol half-life is prolonged in chronic liver disease, but to a lesser extent than antipyrine and lignocaine, and overall its metabolism is quantitatively the same as in healthy subjects (Forrest, Finlayson, Adjepon-Yamoah & Prescott, 1977; Forrest, Adriaenssens, Finlayson & Prescott, 1979). Paracetamol metabolism is also impaired in severe paracetamol poisoning, and prolongation of the plasma half-life is then a reliable index of the severity of liver damage (Prescott & Wright, 1973).

Paracetamol metabolism has been compared in healthy adults given an oral dose of 20 mg/kg and patients with paracetamol poisoning receiving different treatments (Prescott *et al.*, 1979). Plasma and urine concentrations of paracetamol and its metabolites have been measured by high performance liquid chromatography (Adriaenssens & Prescott, 1978). The 20 mg/kg dose is rapidly absorbed and after 3 h the plasma concentrations of glucuronide exceed those of the parent drug (Figure 1). There is a similar relationship between the plasma concentrations of paracetamol and its glucuronide conjugate in patients with paracetamol poisoning without liver damage, but in those who developed severe liver damage (plasma aminotransferases > 1,000 IU/l) paracetamol metabolism is impaired, the half-life is prolonged and glucuronide concentrations are lower than those of the unchanged drug at all times (Figures 1–3). The impairment of glucuronide conjugation seems to be dependent only on the extent of liver damage and is unrelated to treatment (except insofar that early treatment prevents liver damage).

The sulphate conjugation of paracetamol becomes saturated in adults within the therapeutic dose range (Levy & Yamada, 1971). After a dose of 20 mg/kg, the mean maximum plasma concentration of paracetamol sulphate is about 5 µg/ml, and the concentrations are only slightly higher in untreated poisoned patients. However, patients receiving early treatment with *N*-acetylcysteine and cysteamine show a marked increase in plasma concentrations of the sulphate, and there is a minor delayed increase in those with severe liver damage receiving late treatment (Figures 1–3). These results are consistent with saturation of sulphate conjugation, depletion of inorganic sulphate with large doses of paracetamol, and increased availability of sulphate following early



**Figure 2** Mean plasma concentrations of paracetamol (●) and its sulphate (O) and glucuronide conjugates (Δ) (expressed as paracetamol equivalents) in poisoned patients ( $n=4$ ) without liver damage receiving no treatment (a) and early treatment with *N*-acetylcysteine ( $n=14$ ) and cysteamine ( $n=4$ ). Paracetamol  $t_1$ : a, 3.4 h; b, 3.7 hours.

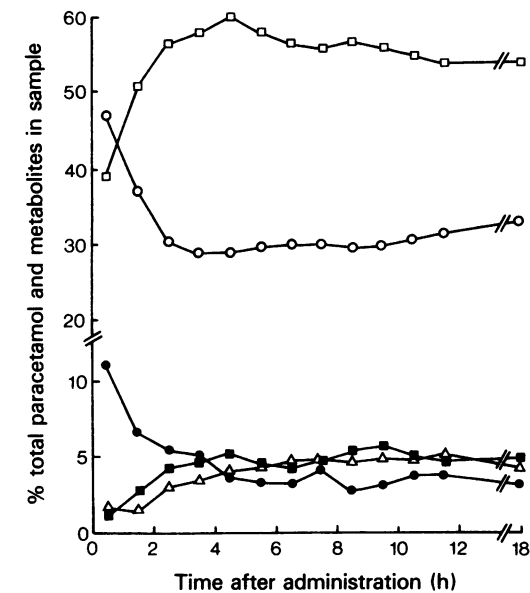


**Figure 3** Mean plasma concentrations of paracetamol (●) and its sulphate (O) and glucuronide conjugates (Δ) (expressed as paracetamol equivalents) in poisoned patients ( $n=5$ ) with severe liver damage receiving no treatment (a) and late (> 10 h) treatment with *N*-acetylcysteine ( $n=9$ ) and cysteamine ( $n=4$ ). Paracetamol  $t_1$ : a, 6.7 h; b, 6.9 hours.

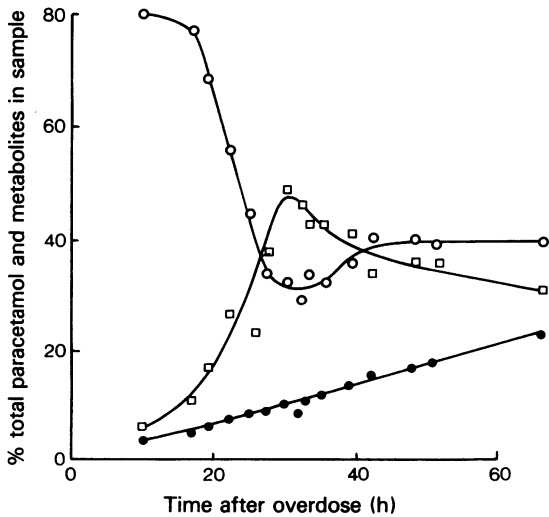
treatment with *N*-acetylcysteine. Intravenous sodium sulphate has a similar effect on sulphate conjugation of paracetamol in rats (Galinsky, Slattery & Levy, 1979).

The urinary excretion of paracetamol and its metabolites after overdosage and after a dose of 20 mg/kg is shown in Table 1. In the latter group

the recovery of sulphate and glucuronide conjugates is about 30% and 55% of the dose, respectively, and excretion is virtually complete within 24 hours. The sulphate conjugate accounts for a very high initial but rapidly falling proportion of the total excreted (Figure 4), again consistent with a limited and decreasing capacity for sulphate conjugation.



**Figure 4** Changes in the mean proportional urinary excretion of paracetamol (●) and its sulphate (○), glucuronide (□), cysteine (Δ) and mercapturic acid conjugates (■) (expressed as paracetamol equivalents) with time after an oral dose of 20 mg/kg in eight healthy subjects.



**Figure 5** Changing pattern of relative urinary excretion of the sulphate (●), glucuronide (○), and cysteine plus mercapturic acid conjugates (□) of paracetamol (expressed as paracetamol equivalents) in a patient with fatal liver damage after paracetamol overdose receiving supportive therapy.

**Table 1** Percentage recovery of paracetamol and its sulphate, glucuronide, cysteine and mercapturic acid conjugates in healthy subjects given an oral dose of 20 mg/kg and in poisoned patients receiving different treatments.

	Treatment	Number of subjects or patients	Paracetamol (%)	Sulphate (%)	Glucuronide (%)	Mercapturate plus cysteine (%)	Mean recovery (g)
Healthy subjects (20 mg/kg)		8	5.0	32.3	54.7	8.0	93%*
Poisoned patients without liver damage	Supportive	9	8.6	9.3	75.3	6.9	10.3
	Cysteamine	15	9.3	11.9	72.4	6.4	14.5
	Methionine	8	8.0	10.1	73.9	8.1	14.5
Poisoned patients with severe liver damage†	NAC	23	11.2	14.5	63.6	10.6	13.4
	Supportive	8	8.7	9.7	66.5	15.2	11.8
	Methionine	3	8.2	9.1	68.9	13.8	13.7
	NAC	8	9.4	13.3	60.9	16.5	13.0

\* % administered dose. NAC, N-acetylcysteine.

† Late (>8 h) treatment with methionine and N-acetylcysteine.

In the poisoned patients only 10–12% of the total excreted is recovered as sulphate and there is a corresponding increase in the excretion of glucuronide and unchanged drug (Table 1). As the amount of paracetamol remaining in the body decreases, there is a progressive increase in the proportion recovered as sulphate (Figure 5) and in some patients it becomes the dominant urinary metabolite.

The production of cysteine and mercapturic acid conjugates of paracetamol is of major toxicological significance (Mitchell *et al.*, 1973; 1974; 1977). About 4% of a dose of 20 mg/kg is recovered in the urine as cysteine, and 4% as mercapturic acid conjugates. Irrespective of treatment, the recovery is virtually the same in the poisoned patients without liver damage, but there is a significant increase in those with severe liver damage (Table 1). The mean total urinary recovery of cysteine and mercapturic acid conjugates is almost twice as high in patients with severe liver damage than in those without (1.95 and 1.13 g, respectively). The peak percentage excretion of the cysteine and mercapturic acid conjugates is usually delayed for about 30 h in patients with severe liver damage, when these two metabolites account for 20–50% of the total excreted (Figure 5).

Treatment with cysteamine and methionine has little if any effect on the pattern of excretion of paracetamol metabolites but sulphate, cysteine and mercapturic acid conjugates are clearly increased by *N*-acetylcysteine (Table 1).

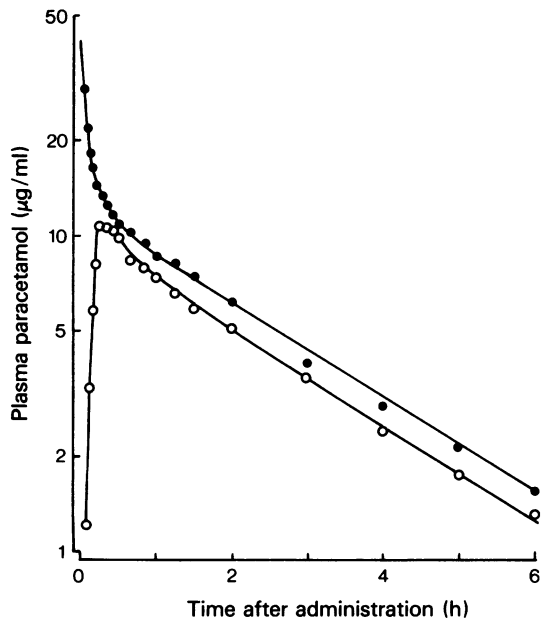
#### Renal excretion

The mean renal clearance of paracetamol in the healthy subjects given 20 mg/kg was 13 ml/minute. A similar value has been reported in a previous study, and the clearance depends on urine flow rate but not pH (Prescott & Wright, 1973). Paracetamol seems to be filtered at the glomerulus with subsequent extensive tubular reabsorption.

The mean renal clearances of paracetamol sulphate and glucuronide are 166 and 130 ml/min, respectively, and there is no correlation with urine flow or pH. These findings indicate active renal tubular secretion, and similar mechanisms of the renal excretion of paracetamol and these conjugates have been demonstrated in dogs (Duggin & Mudge, 1975). The plasma half-life of paracetamol is not increased in patients with impaired renal function, but there is accumulation and retention of conjugates (Prescott, 1969; Øie, Lowenthal, Briggs & Levy, 1975).

#### Kinetics

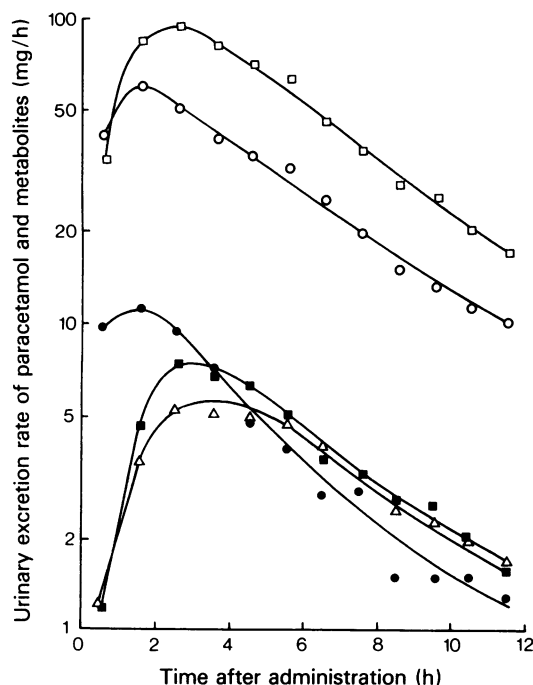
The kinetics of paracetamol absorption, distribution and elimination have been studied by many



**Figure 6** Mean plasma concentrations of paracetamol in four healthy subjects following intravenous (●) and oral doses (○) of 12 mg/kg on separate occasions.

investigators (Nelson & Morioka, 1963; Cummings, King & Martin, 1967; Levy & Yamada, 1971; Prescott & Wright, 1973; Øie *et al.*, 1975; Clements & Prescott, 1976; Briant *et al.*, 1976; Rawlins, Henderson & Hijab, 1977; Clements, Heading, Nimmo & Prescott, 1978; Slattery & Levy, 1979; and others). A new pharmacokinetic model has recently been developed to take into account the critical effect of variation in gastric emptying rate on paracetamol absorption in man. With this model there is excellent agreement between observed and calculated plasma paracetamol concentrations with different rates and patterns of gastric emptying. The mean half-time for paracetamol absorption from the small intestine is less than 7 min (Clements *et al.*, 1978).

After the intravenous injection of 12 mg/kg of paracetamol over 2 min in healthy adults, plasma concentrations decrease rapidly during the first hour followed by a slower elimination phase (Figure 6). The data are consistent with a two-compartment open model, and the results of conventional pharmacokinetic analysis are summarized in Table 2. The volume of distribution and total body clearance in a 70 kg adult are about 65 l and 380 ml/min, respectively. In the same subjects subsequently given the same dose of paracetamol orally in solution, absorption is very rapid with the mean peak plasma concentration occurring at 15 min; after a short distributive phase, concentrations decline in parallel



**Figure 7** Mean urinary excretion rates of paracetamol (●) and its sulphate (○), glucuronide (□), cysteine (Δ) and mercapturic acid conjugates (■) (expressed as paracetamol equivalents) in eight healthy subjects after an oral dose of 20 mg/kg.

with those after intravenous injection (Figure 6). Mean systemic availability of paracetamol calculated from the relative areas under the intravenous and oral plasma-concentration-time curves is 76%. Similar results have been reported by others, and the 'first-pass' metabolism of paracetamol may be dose-dependent and inducible (Rawlins *et al.*, 1977; Perucca & Richens, 1979).

The urinary excretion of paracetamol and its

sulphate, glucuronide, cysteine and mercapturic acid conjugates in healthy subjects given an oral dose of 20 mg/kg is shown in Figure 7. When the data are plotted as 'sigma-minus' values (Cummings *et al.*, 1967), the regression lines become approximately parallel after 3–4 hours.

### Phenacetin

Phenacetin (acetophenetidine) is highly lipid-soluble with limited aqueous solubility, and its oral absorption is highly dependent on formulation factors such as particle size (Prescott, Steel & Ferrier, 1970). The drug is extensively metabolized and less than 0.5% of a dose is recovered unchanged in the urine. The major metabolic route is O-dealkylation to paracetamol (60–80%), and minor pathways include deacetylation and hydroxylation to form *p*-phenetidine, 2-hydroxyphenetidine, 2- and 3-hydroxyphenacetin and *N*-hydroxyphenacetin. These metabolites, together with the previously mentioned metabolites of paracetamol, are excreted largely as conjugates in the urine (Brodie & Axelrod, 1949; Jagenburg & Toczko, 1964; Büch, Pfleger, Rummel, Ullrich, Hey & Staudinger, 1967; Prescott, 1969; Raaflaub & Dubach, 1969; Nery, 1971; Uehleke, 1973; Smith & Timbrell, 1974; Klutch *et al.*, 1978).

There is extensive 'first-pass' metabolism of phenacetin by the small intestinal mucosa and liver, which is inducible by polycyclic hydrocarbons and cigarette smoking (Kuntzman, Pantuck, Kaplan & Conney, 1977). The hydroxylation of phenacetin is under genetic control and there are marked species differences in the metabolism of the drug (Smith & Timbrell, 1974). In animals and in man the deacetylation of phenacetin is dose-dependent with a marked relative increase in the production of *p*-phenetidine and 2-hydroxyphenetidine at higher doses (Raaflaub & Dubach, 1969; Smith & Timbrell, 1974). The plasma half-life of phenacetin in man is about 1 h (Prescott, Sansur, Levin & Conney, 1968;

**Table 2** Pharmacokinetic variables in four healthy adult males given paracetamol 12 mg/kg intravenously and orally on separate occasions.

	Orally	Intravenously
Elimination half-life (h)	1.97±0.3	1.98±0.3
Distribution half-life (h)	—	0.13±0.05
Total body clearance (ml kg <sup>-1</sup> min <sup>-1</sup> )	—	5.45±0.2
VD <sub>c</sub> (ml/kg)	—	509±68
VD <sub>ss</sub> (ml/kg)	—	897±94
AUC <sub>∞</sub> (μg ml <sup>-1</sup> h <sup>-1</sup> )	28.0±5.8	36.7±1.2
Systemic availability	76±13%	—

Values given are mean ±s.d.

VD<sub>c</sub>, Volume of central compartment.

VD<sub>ss</sub>, Volume of central and peripheral compartments.

Kuntzman *et al.*, 1977).

The toxicity of phenacetin is related to its metabolism. Methaemoglobinaemia has been attributed to the formation of *p*-phenetidine and *N*-hydroxy metabolites and is increased by microsomal enzyme induction (Uehleke, 1973). Like paracetamol, phenacetin is converted to a reactive alkylating metabolite which binds covalently to hepatic and renal tubular cell proteins causing necrosis (Mitchell *et al.*, 1977). The reactive metabolite is probably a benzoquinone-imine derived from *N*-hydroxyphenacetin (Nery, 1971; Calder, Creek, Williams, Funder, Green, Ham & Tange, 1973).

Phenacetin has been universally and uncritically implicated in the development of tumours of the

renal pelvis, ureters and bladder in patients with analgesic nephropathy. Although chronic toxicity studies of phenacetin have failed to produce similar tumours in animals, many carcinogenic aromatic amines are activated by *N*-hydroxylation and recent studies have shown that the *N*-*O*-sulphate and glucuronide conjugates of *N*-hydroxyphenacetin are potent alkylating agents (Mulder, Hinson & Gillette, 1977; 1978). These unstable conjugates are concentrated in the urine and liable to enzymic hydrolysis by the uroepithelium and possibly bacteria. Unlike its polar metabolites, phenacetin is extensively re-absorbed by the renal tubules. There is no significant corticomedullary concentration gradient and the ratio of urine to plasma concentrations is essentially unity (Duggin & Mudge, 1976).

## References

- ADRIAENSSENS, P.I. & PRESCOTT, L.F. (1978). High performance liquid chromatographic estimation of paracetamol metabolites in plasma. *Br. J. clin. Pharmac.*, **6**, 87-88.
- ANDREWS, R.S., BOND, C.C., BURNETT, J., SAUNDERS, A. & WATSON, K. (1976). Isolation and identification of paracetamol metabolites. *J. Int. med. Res.*, **4**, suppl. 4, 34-39.
- LOSOWSKY, M.S. (1979). The gastrointestinal absorption of paracetamol in the rat. *J. Pharm. Pharmac.*, **31**, 157-160.
- BRIANT, R.H., DORRINGTON, R.E., CLEAL, J. & WILLIAMS, F.M. (1976). The rate of acetaminophen metabolism in the elderly and the young. *J. Am. Geriatric Soc.*, **24**, 359-361.
- BRODIE, B.B. & AXELROD, J. (1949). The fate of acetophenetidin (phenacetin) in man and methods for the estimation of acetophenetidin and its metabolites in biological material. *J. Pharmac. exp. Therap.*, **97**, 58-67.
- BÜCH, H., PFLEGER, K., RUMMEL, W., ULLRICH, V., HEY, D. & STAUDINGER, H. (1967). Untersuchungen über den oxydativen Stoffwechsel des Phenacetins bei der Ratte. *Biochem. Pharmac.*, **16**, 2247-2256.
- CALDER, I.C., CREEK, M.J., WILLIAMS, P.J., FUNDER, C.C., GREEN, C.R., HAM, K.N. & TANGE, J.D. (1973). *N*-Hydroxylation of *p*-Acetophenetidine as a factor in nephrotoxicity. *J. med. Chem.*, **16**, 499-502.
- CLEMENTS, J.A., HEADING, R.C., NIMMO, W.S. & PRESCOTT, L.F. (1978). Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmac. Ther.*, **24**, 420-431.
- CLEMENTS, J.A. & PRESCOTT, L.F. (1976). Data point weighting in pharmacokinetic analysis: intravenous paracetamol in man. *J. Pharm. Pharmac.*, **28**, 707-709.
- CUMMINGS, A.J., KING, M.L. & MARTIN, B.K. (1967). A kinetic study of drug elimination: the excretion of paracetamol and its metabolites in man. *Br. J. Pharmac. Chemother.*, **29**, 150-157.
- DUGGIN, G.G. & MUDGE, G.H. (1975). Renal tubular transport of paracetamol and its conjugates in the dog. *Br. J. Pharmac.*, **54**, 359-366.
- DUGGIN, G.G. & MUDGE, G.H. (1976). Phenacetin: renal tubular transport and intrarenal distribution in the dog. *J. Pharmac. exp. Ther.*, **199**, 10-16.
- FORREST, J.A.H., ADRIAENSSENS, P.I., FINLAYSON, N.D.C. & PRESCOTT, L.F. (1979). Paracetamol metabolism in chronic liver disease. *Eur. J. clin. Pharmac.*, **15**, 427-431.
- FORREST, J.A.H., FINLAYSON, N.D.C., ADJEPON-YAMOA, K.K. & PRESCOTT, L.F. (1977). Antipyrine, paracetamol, and lignocaine elimination in chronic liver disease. *Br. med. J.*, **1**, 1384-1387.
- GALINSKY, R.E., SLATTERY, J.T. & LEVY, G. (1979). Effect of sodium sulphate on acetaminophen elimination by rats. *J. pharm. Sci.*, **68**, 803-805.
- GAZZARD, B.G., FORD-HUTCHINSON, A.W., SMITH, M.J.H. & WILLIAMS, R. (1973). The binding of paracetamol to plasma proteins of man and pig. *J. Pharm. Pharmac.*, **25**, 964-967.
- HEADING, R.C., NIMMO, J., PRESCOTT, L.F. & TOTHILL, P. (1973). The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmac.*, **47**, 415-421.
- JAGENBURG, O.R. & TOCZKO, K. (1964). The metabolism of acetophenetidine. Isolation and characterization of S-(1-acetamido-4-hydroxyphenyl)-cysteine, a metabolite of acetophenetidine. *Biochem. J.*, **92**, 639-643.
- JONES, D.P., SUNDBY, G.-B., ORMSTAD, K. & ORRENIUS, S. (1979). Use of isolated kidney cells for study of drug metabolism. *Biochem. Pharmac.*, **28**, 929-935.
- JOSTING, D., WINNE, D. & BOCK, K.W. (1976). Glucuronidation of paracetamol, morphine and 1-naphthol in the rat intestinal loop. *Biochem. Pharmac.*, **25**, 613-616.
- KLUTCH, A., LEVIN, W., CHANG, R.L., VANE, F. & CONNEY, A.H. (1978). Formation of a thiomethyl metabolite of phenacetin and acetaminophen in dogs and man. *Clin. Pharmac. Therap.*, **24**, 287-293.
- KUNTZMAN, R., PANTUCK, E.J., KAPLAN, S.A. & CONNEY, A.H. (1977). Phenacetin metabolism: Effect of hydrocarbons and cigarette smoking. *Clin. Pharmac. Therap.*,

- 22, 757-764.
- LEVY, G., KHANNA, N.N., SODA, D.M., TSUZUKI, O. & STERN, L. (1975). Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and d-glucuric acid excretion. *Pediatrics*, **55**, 818-825.
- LEVY, G. & YAMADA, H. (1971). Drug biotransformation interactions in man III: acetaminophen and salicylamide. *J. pharm. Sci.*, **60**, 215-221.
- McGILVERAY, I.J. & MATTOCK, G.L. (1972). Some factors affecting the absorption of paracetamol. *J. Pharm. Pharmac.*, **24**, 615-619.
- MILLER, R.P., ROBERTS, R.J. & FISCHER, L.J. (1976). Acetaminophen elimination kinetics in neonates, children, and adults. *Clin. Pharmac. Therap.*, **19**, 284-294.
- MITCHELL, J.R., JOLLOW, D.J., POTTER, W.Z., DAVIS, D.C., GILLETTE, J.R. & BRODIE, B.B. (1973). Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. *J. Pharmac. exp. Therap.*, **187**, 185-194.
- MITCHELL, J.R., McMURTRY, R.J., STATHAM, C.N. & NELSON, S.D. (1977). Molecular basis for several drug-induced nephropathies. *Am. J. Med.*, **62**, 518-526.
- MITCHELL, J.R., THORGEIRSSON, S.S., POTTER, W.Z., JOLLOW, D.J. & KEISER, H. (1974). Acetaminophen-induced hepatic injury: Protective role of glutathione in man and rationale for therapy. *Clin. Pharmac. Therap.*, **16**, 676-684.
- MULDER, G.J., HINSON, J.A. & GILLETTE, J.T. (1977). Generation of reactive metabolites of N-hydroxyphenacetin by glucuronidation and sulfation. *Biochem. Pharmac.*, **26**, 189-196.
- MULDER, G.J., HINSON, J.A. & GILLETTE, J.R. (1978). Conversion of the N-O-glucuronide and N-O-sulfate conjugates of N-hydroxyphenacetin to reactive intermediates. *Biochem. Pharmac.*, **27**, 1641-1649.
- NELSON, E. & MORIOKA, T. (1963). Kinetics of the metabolism of acetaminophen by humans. *J. pharm. Sci.*, **52**, 864-868.
- NERY, R. (1971). Some new aspects of the metabolism of phenacetin in the rat. *Biochem. J.*, **122**, 317-326.
- NIMMO, J., HEADING, R.C., TOTHILL, P. & PRESCOTT, L.F. (1973). Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption. *Br. med. J.*, **1**, 587-589.
- NIMMO, W.S., HEADING, R.C., WILSON, J., TOTHILL, P. & PRESCOTT, L.F. (1975). Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br. J. clin. Pharmac.*, **2**, 509-513.
- NIMMO, W.S. & PRESCOTT, L.F. (1978). The influence of posture on paracetamol absorption. *Br. J. clin. Pharmac.*, **5**, 348-349.
- ØIE, S., LOWENTHAL, D.T., BRIGGS, W.A. & LEVY, G. (1975). Effect of hemodialysis on kinetics of acetaminophen elimination by anephric patients. *Clin. Pharmac. Therap.*, **18**, 680-686.
- PERUCCA, E. & RICHENS, A. (1979). Paracetamol disposition in normal subjects and in patients treated with antiepileptic drugs. *Br. J. clin. Pharmac.*, **7**, 201-206.
- PRESCOTT, L.F. (1969). The metabolism of phenacetin in patients with renal disease. *Clin. Pharmac. Therap.*, **10**, 383-394.
- PRESCOTT, L.F. (1974). Gastrointestinal absorption of drugs. *Med. Clin. N. Am.*, **58**, 907-916.
- PRESCOTT, L.F., ILLINGWORTH, R.N., CRITCHLEY, J.A.J.H., STEWART, M.J., ADAM, R.D. & PROUDFOOT, A.T. (1979). Intravenous N-acetylcysteine — the treatment of choice for severe paracetamol poisoning. *Br. med. J.*, **2**, 1097-1100.
- PRESCOTT, L.F., SANSUR, M., LEVIN, W. & CONNEY, A.H. (1968). The comparative metabolism of phenacetin and N-acetyl-p-aminophenol in man, with particular reference to effects on the kidney. *Clin. Pharmac. Therap.*, **9**, 605-614.
- PRESCOTT, L.F., STEEL, R.F. & FERRIER, W.R. (1970). The effects of particle size on the absorption of phenacetin in man. *Clin. Pharmac. Therap.*, **11**, 496-504.
- PRESCOTT, L.F. & WRIGHT, N. (1973). The effects of hepatic and renal damage on paracetamol metabolism and excretion following overdosage. A pharmacokinetic study. *Br. J. Pharmac.*, **49**, 602-613.
- RAAFLAUB, H. & DUBACH, U.C. (1969). Dose-dependent change in the pattern of phenacetin metabolism in man and its possible significance in analgesic nephropathy. *Klin. Wschr.*, **47**, 1286-1287.
- RAWLINS, M.D., HENDERSON, D.B. & HIJAB, A.R. (1977). Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. *Eur. J. clin. Pharmac.*, **11**, 283-286.
- SLATTERY, J.T. & LEVY, G. (1979). Acetaminophen kinetics in acutely poisoned patients. *Clin. Pharmac. Therap.*, **25**, 184-195.
- SMITH, R.L. & TIMBRELL, J.A. (1974). Factors affecting the metabolism of phenacetin. I. Influence of dose, chronic dosage, route of administration and species on the metabolism of [ $^{14}\text{C}$ -acetyl]phenacetin. *Xenobiotica*, **4**, 489-501.
- UEHLEKE, H. (1973). Biochemical pharmacology and toxicology of phenacetin. In *International Symposium on Problems of Phenacetin Abuse*. Ed. Haschek, H. Pp. 31-44. Vienna: Facta Publication.